American Journal of Medical Genetics 61:45–48 (1996)

Terminal Deletion of the Long Arm of Chromosome 3 [46,XX,del(3)(q27→qter)]

David Chitayat, Riyana Babul, Meredith M. Silver, Venita Jay, Ikuko E. Teshima, Paul Babyn, and Laurence E. Becker

The Division of Clinical Genetics (D.C., R.B., I.E.T.), Pathology (M.M.S., L.E.B., V.J.), and Diagnostic Imaging (P.B.), The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

We report on a terminal deletion of the long arm of chromosome 3 [46,XX,del(3)(q27→qter)] in a female newborn infant who died 45 hours after delivery and had multiple congenital abnormalities including bilateral anophthalmia, congenital heart disease, and abnormal genitalia. The findings are compared to those of four previously reported cases with terminal del (3q).

KEY WORDS: terminal deletion 3q, MCA syndrome, anophthalmia, genital abnormality

INTRODUCTION

Only four cases of terminal deletion of the long arm of chromosome 3 are reported [Alvarez Arratia et al., 1984; Sargent et al., 1985; Brueton et al., 1989; Jokiaho et al., 1989]. The findings in the four cases differ considerably and are thus insufficient for delineating a specific syndrome. However, Alvarez Arratia et al. [1984], reported a case with del(3)(q28) with clinical findings similar to those seen in our patient. The neuro- and ophthalmo-pathological findings in our case suggest that genes important for the embryogenesis of the eyes and brain are located at the distal segment of 3q.

CLINICAL REPORT

The infant was born to a 24-year-old G2P1 mother from Ghana who had a 4.5-year-old healthy son from a previous marriage. Her family history was non-contributory and her karyotype, 46,XX. The father of the proposita was also from Ghana and has a healthy son and daughter from a previous marriage. No information was available about his family and chromosome analysis was not done on him. The couple was non-consanguineous.

The pregnancy was uncomplicated except for vaginal spotting during the first trimester. Fetal ultrasound (U/S) study was done at 20 weeks of gestation and was interpreted as normal. Fetal movements were first felt at 24 weeks and were feeble. Delivery was at 42 weeks of gestation, spontaneous and vaginal with vertex presentation. The Apgar scores were 5 and 6 at 1 and 5 minutes, respectively. The newborn infant developed respiratory distress and was intubated orally because both posterior choanae were obstructed. On physical examination, weight was 1.934 kg, length was 46 cm, and head circumference (OFC) was 30 cm (all <3rd centile). The anterior fontanelle was large (2.5 × 2.5 cm) with a high and triangular forehead and frontal bossing. The face was triangular in shape with hypoplastic supraorbital ridges and short palpebral fissures (Fig. 1). The orbits were shallow and no ocular structures could be seen. A horizontal crease was present over the nasal bridge and the nose was short, bulbous with a flattened tip. Malar areas were hypoplastic, the philtrum was short, and the ears appeared low set. Micrognathia and an intact palate were noted. A cardiac systolic murmur was heard maximal along the left sternal border; the sternum was short. The abdomen was tender and distended, the labia majora were hypoplastic, and the anus was atretic. The hands showed bilaterally adducted and digitalized thumbs and tapering fingers, with clinodactyly of the 5th fingers and hyperconvex nails (Fig. 1). The great toes were shorter than the 2nd toes and the toe nails were deep set and hypoplastic.

Chromosome analysis showed a terminal deletion of the long arm of chromosome 3 [46,XX,del(3)(q27>qter)] (an alternate interpretation of an interstitial deletion of 3q26.2-3q29 and 46,XX,−3, +der(3)t(3;?)(q27;?)] with monosomy 3q and simultaneous trisomy for a telomeric region of unknown origin, could not be ruled out)] (Fig. 2).

Echocardiography documented a patent ductus arteriosus and pulmonary hypertension. Abdominal ultrasound (U/S) demonstrated a midline mass with low level uniform echogenicity compatible with distended uterus and/or vagina. There were small echogenic kidneys with moderate calyceal dilatation and a distended bowel. Head U/S study showed an enlarged prepontine cistern or an arachnoid cyst in this region (Fig. 3).

Skeletal survey showed microcephaly with small orbits and hypoplastic maxilla. The pelvis was contracted with narrow and tall iliac wings and the right ulna was short. The distal phalanges of both thumbs were hypoplastic

Received for publication March 29, 1995; revision received July 12, 1995.

Address reprint requests to Dr. David Chitayat, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada, M5G 1X8.

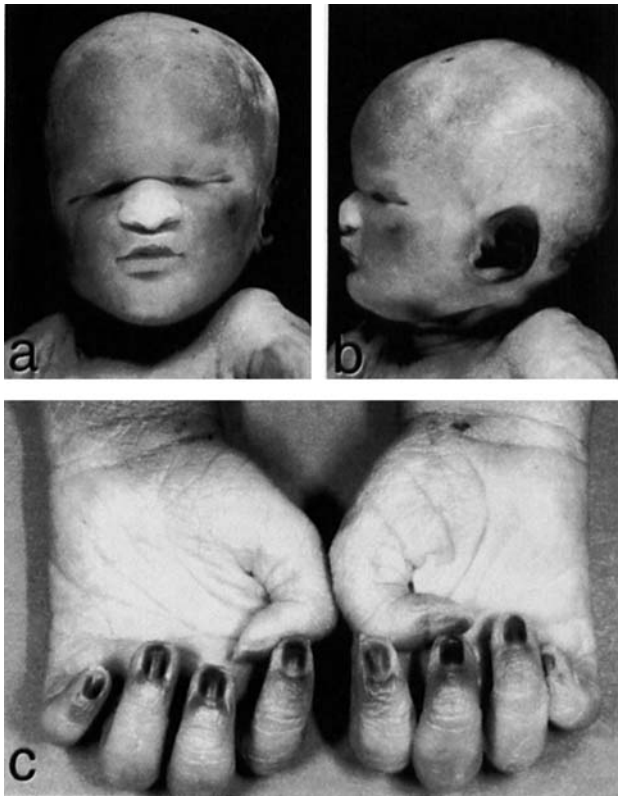

Fig. 1. Frontal (**a**) and side view (**b**) demonstrating hypoplastic supraorbital ridges with short palpebral fissures, shallow orbits, a horizontal crease over the nasal bridge, and bulbous nose. In (**c**) the patient's hands showing bilateral adducted and digitalized thumbs, tapering fingers, and hyperconvex nails.

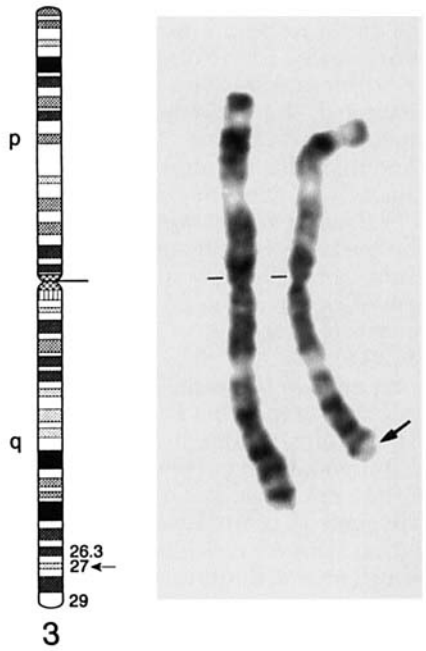

Fig. 2. Chromosome 3 pair. To the left is an idiogram of the normal chromosome 3 at the 850 band stage of resolution [adapted from Francke, 1994]. The normal 3 is on the left and the (del)(3)(q27) is on the right (arrow).

Fig. 3. Cranial U/S. Sagittal midline view showing an anechogenic space in keeping with an enlarged prepontine cistern or an arachnoid cyst (arrow).

and the sternum, distal femora, proximal tibia and pubis showed delayed ossification. The baby died at 2 days.

Autopsy confirmed the presence of minor facial anomalies as described above (Fig. 1), a large foramen ovale and ductus arteriosus. The diaphragm was normal and the lungs were hypoplastic. The abdomen showed malrotated, non-fixed and distended bowel with the ileocecal region being in mid abdomen, as well as rectal agenesis and anal atresia. External genitalia were phenotypically female, with hypoplasia of the labia. The vagina was "atretic" above the introitus and the upper vagina and uterus were hugely distended with mucoid fluid (Fig. 4).

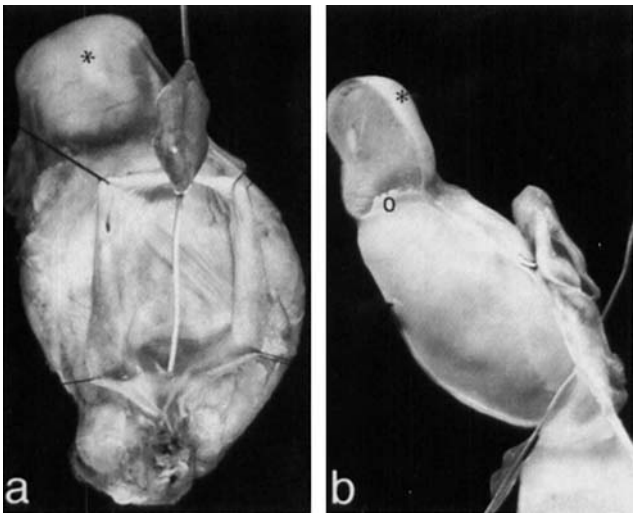

Fig. 4. The highly dilated uterus (* on fundus) and upper vagina is seen behind the opened bladder in (**a**) and to its left in the bivalved specimen in (**b**); (O) indicates the external cervical os. A probe lies within a vesico-vaginal fistula connecting the anterior part of the vagina and the urinary bladder and opened in the trigone between the two ureteric orifices.

TABLE I. Clinical Findings and Cytogenetic Results in Patients with Terminal Deletion 3q*

	Alvarez Arratia et al. [1984]	Sargent et al. [1989]	Brueton et al. [1989]	Jokiaho et al. [1989]	Present case
Deleted segment	3q28-qter	3q27-qter	3q27-qter	3q27-qter	3q27-qter
Sex	F	M	M	F	F
Gestation	Term	37 weeks	Term	Term	42 weeks
IUGR	+	−	−	−	+
Microcephaly	+	+	−	−	+
Skull shape	Dolichocephaly	Trigonocephaly	Normal	Normal	
Dolichocephaly					
Sparse hair	+	−	−	−	NR
Face					
Snophrys	−	+	−	−	−
Epicanthic folds	?	+	−	+	NR
Hypoplastic supraorbital ridges	+	?	−	+	+
Short palpebral fissures	+	?	−	+	+
Microphthalmia/ anophthalmia	+	−	−	−	+
Strabismus	?	?	+	−	NR
Broad nose	+	+	+	+	+
Lip and palate	Bilat cleft lip and palate	−	−	−	−
Telecanthus	?	+	−	+	NR
Deep sulcus across the nasal bridge	+	−	−	−	+
Ears	Low set, malformed	Low set	Small, posteriorly rotated	Low set	Posteriorly rotated & small
Philtrum	?	?	long, smooth	?	NA
Retro-micrognathia	+	−	−	+	+
Other anomalies					
Short neck	+	+	−	+	+
Thoracic abnormalities	Pectus carinatum, 13 thoracic vertebrae and ribs	−	Kyphosis	−	−
Cardiac defect	+	−	−	−	+
Limb anomalies	+	−	−	Fingers and thumbs were held flexed	Bilat and digitalized adducted thumbs, tapering fingers, clinodactyly of 5th fingers
Anal atresia	−	−	−	−	+
Urogenital anomalies	?	−	−	−	+
Brain CT scan/US findings	?	Cerebral atrophy, DWM, absence of cerebellar vermis, ventricular dilation, posterior fossa cyst	Normal	Meningocele	Suprasellar-cystic lesion
Failure to thrive	+	+	+	−	NR
Short stature	+	−	+	−	−
Tone	Decreased	Decreased	Decreased	Increased	Increased
Development delay	+	+	+	+	NR
Survival	Died at 3 months	Died at 26 months	Alive and well	Alive and well	Died at 2 days

*+/−, Presence/absence of the sign; NR, not relevant; DWM, Dandy-Walker malformation; NA, not available.

A fistula connected the anterior part of the vagina and the urinary bladder and opened in the trigone between the two ureteric orifices. The ureters were compressed by the hydrocolpos at the pelvic brim resulting in hydronephrosis. The kidneys were hypoplastic and weighed half the expected weight, and had dilated calyces. Foci of nephrogenesis were present in the subcapsular zone (abnormal beyond 36 weeks gestation) but no obstructive renal dysplasia was noted. The adrenals were small and weighed less than half the expected weight with defi-

cient fetal adrenal cortex suggesting the possibility of a lesion in the hypothalamic-pituitary axis. However, neuropathological examination showed a small but normally formed brain with thin and transparent leptomeninges. The cranial nerves were normal apart from hypoplastic optic nerves; olfactory nerves were present. The ventricular system, cerebellum and pituitary gland were normal. No arachnoid cyst was found thus the ultrasound finding was reinterpreted as representing an enlargement of the prepontine cistern.

Ophthalmopathological examination showed no definitive contents in either orbit. The orbits contained extraocular muscles and their innervating nerves, foci of extramedullary hematopoiesis, a remnant ciliary ganglion, nests of lacrimal gland tissue, and conjuctival lining. A focus of uveal melanocytes and retinal pigment epithelium was seen. No other ocular layers were identified and optic nerves were absent. The findings were those of bilateral anophthalmia.

DISCUSSION

Terminal deletion of the long arm of chromosome 3 is a rare finding and to the best of our knowledge only four cases with this chromosome abnormality have been reported (Table I), the first by Alvarez Arratia et al. [1984]. This patient presented with intrauterine growth retardation, microcephaly, bilateral microphthalmos, bilateral cleft lip and palate, with deep sulcus across the nasal bridge, apparently low-set malformed ears, short neck, congenital heart disease, and abnormalities of the hands and feet. Because an autopsy was not done, information regarding internal abnormalities was not available. In a report on trigonocephaly, Sargent et al. [1985] reported a case with terminal deletion of 3q [46,XY,del(3)(pter→q27:)] with trigonocephaly, failure to thrive, microcephaly, minor facial anomalies, and developmental delay. The brain CT scan showed a Dandy-Walker malformation and cerebral atrophy. In 1989, Jokiaho et al. [1989] reported on a case with terminal deletion of 3q [46,XX,del(3)(q27→qter)] in a female infant with small mouth and eyes, thin lips, short palpebral fissures, short neck, apparently low-set ears, overlapping second toes, and adducted thumbs. Also she had a parietal meningocele and miliaria rubra-like skin lesions which raised the suggestion of chromosome mosaicism as reported previously with pigmentary skin lesions [Thomas et al., 1989].

In 1989, Brueton et al. [1989] reported on a male infant with a terminal deletion of 3q [46,XY,del(3)(pter→q27:)] and minor facial anomalies, developmental delay, hypotonia, mild thoracic scoliosis, and normal brain CT scan. The authors could not exclude a possibility that the patient's karyotype was 46,XY,−3,+der(3),t(3;?)(q27;?)] with monosomy 3q and simultaneous trisomy for a telomeric region of unknown origin.

Although all of the above reported patients have deletion of the distal segment of 3q, most of the findings in common (developmental delay, growth retardation, hypotonia, and ear abnormalities) are non-specific. However, the cases reported by Brueton et al. [1989] and Jokiaho et al. [1989] had similar facial changes; both survived and did relatively well. Our case resembles that reported by Alvarez Arratia et al. [1984] since both had bilateral microphthalmia or anophthalmia with short palpebral fissures and high nasal bridge with deep sulcus across the nasal bridge.

Microphthalmia has been reported in many chromosome abnormalities, the most common being trisomy 13, trisomy 18, del(18p), del(13q), and del(4p) [Warburg, 1993]. The chromosome deletions associated with microphthalmia raise the possibility that microphthalmia may be caused by haploinsufficiency of a gene with a major role in eye development. The recent discovery that the gene for dominant optic atrophy, type Kjer [McKusick number 165500] maps to 3q28-qter Eiberg et al. [1993] raises the possibility that this gene may play a major role in the embryogenesis of the eye. Deletion of this gene may be the cause of the microphthalmia/anophthalmia found in our patient and the patient reported by Alvarez Arratia et al. [1984]. However, no such eye abnormality was reported in the cases by Brueton et al. [1989] and Jokiaho et al. [1989] with terminal deletion of 3q.

Our case provides additional evidence that gene or genes contributing to normal brain and eye development are located at the distal end of 3q. Hence, this region should be investigated in genetic conditions associated with anophthalmia/microphthalmia.

REFERENCES

Alvarez Arratia AMC, Rivera H, Moller M, Valdivia A, Vigueras A, Cantú JM (1984): De novo del(3)(q2800). Ann Genet 27:109–111.

Brueton LA, Barber JCK, Huson SM, Winter RM (1989): Partial monosomy 3q in a boy with short stature, developmental delay, and mild dysmorphic features. J Med Genet 26:729–730.

Eiberg H, Kjer B, Kjer P, Rosenberg T (1993): Dominant optic atrophy (OPA1) mapped to chromosome 3q region. I. linkage analysis. Hum Mol Genet 3:977–980.

Francke U (1994): Digitized and differentially shaded human ideograms for genome applications. Cytogenet Cell Genet 65:206–219.

Jokiaho I, Salo A, Niemi K-M, Blomstedt GC, Pihkala J (1989): Deletion 3q27→3qter in an infant with mild dysmorphism, parietal meningocele, and neonatal miliaria rubra-like lesions. Hum Genet 83:302–304.

Sargent C, Burn J, Baraitser M, Pembrey ME (1985): Trigonocephaly and Opitz C syndrome. J Med Genet 22:39–45.

Thomas IT, Frías JL, Cantú ES, Lafer CZ, Flannery DB, Graham JG Jr (1989): Association of pigmentary anomalies with chromosomal and genetic mosaicism and chimerism. Am J Hum Genet 45: 193–205.

Warburg M (1993): Classification of microphthalmos and coloboma [review]. J Med Genet 30:664–669.